Progression Rates and Sample Size Estimates for Primary Progressive Multiple Sclerosis Based on the CLIMB Study Population

Abstract:

Background: The clinical trial design for primary progressive multiple sclerosis (PPMS) requires understanding of disability progression in modern patient cohorts.

Objective: To characterize demographic and clinical characteristics of the CLIMB study (Boston, MA) PPMS patient cohort and assess rate of disability progression.

Methods: We studied PPMS (n = 73) and relapsing-onset MS (ROMS) patients (n = 1541) enrolled in CLIMB, a longitudinal study of MS patients at the Brigham and Women's Hospital (Boston, MA). Disability progression for each group was compared using interval-censored survival analysis and time to six-month sustained progression.

Results: The PP group had 1.09:1 male:female ratio compared to 1:2.89 for the RO group and greater mean age of onset (PP: 44.4+/-9.6; RO: 32.7+/-9.9; $p<0.0001$). Motor symptoms at onset and first symptoms localized to spinal cord were each strongly associated with PPMS ($p<0.001$). Median time from onset to EDSS 6.0 was faster in PPMS ($p<0.001$). PPMS patients progressed faster to EDSS 3 ($p<0.001$) and from EDSS 3 to 6 ($p<0.001$). Median time to sustained progression in the PP group was 4.85 years (95% CI 2.83-8.35), significantly faster than the RO group ($p<0.001$).

Conclusions: Our modern PPMS cohort is demographically similar to previously studied cohorts. PPMS is associated with faster disability accrual than ROMS. Current real-world observations of time to sustained progression will inform design of new clinical trials for PPMS.

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Glossary:

CLIMB	"Comprehensive Longitudinal Investigation of Multiple Sclerosis at the Brigham and Women's Hospital"
EDSS	Expanded Disability Status Scale
MS	Multiple sclerosis
MSSS	Multiple Sclerosis Severity Score
PP	Primary progressive
PR	Progressive-relapsing
RO	Relapsing-onset
RR	Relapsing remitting
SP	Secondary progressive

Introduction:

Multiple sclerosis (MS), the most common cause of neurological disability among young adults in the Western world, is a disease with significant heterogeneity in presentation and characterized by inflammation and chronic degeneration in the central nervous system (CNS).(1) Combinations and permutations of the two fundamental clinical phenomena of MS, acute relapse and persistent disease progression (permanent disability accrual), result in varied clinical course patterns that form the main clinical subtypes of MS (2): relapsing-remitting (RRMS), secondary progressive (SPMS), primary progressive (PPMS), and progressive-relapsing (PRMS).

A majority of MS patients begin with RRMS, characterized by distinct disease relapses with full recovery or some residual deficit upon recovery and progression-free periods between relapses.(3) 2-3% of RRMS patients annually convert to SPMS (4), which is characterized by progression in the presence or absence of relapses, remissions, and plateaus.(3) Because RR and SPMS share the same relapsing-remitting presentation at disease onset, they are together referred to as relapsing-onset MS (ROMS). PPMS is found in approximately 10-15% of the MS population, has the worst prognosis of MS subtypes, and is characterized by continued worsening of disease from onset with occasional minor improvements or plateaus.(3, 5) PRMS, which presents as progressive disease from onset with superimposed distinct relapses, is quite rare and is frequently considered to share a similar natural history to PPMS.(4, 6)

Despite the broad spectrum of clinical manifestations, it is generally accepted that MS subtypes derive from common disease mechanisms. Supporting this notion, a multicenter genome-wide association study found numerous genetic associations with MS as a whole but no differences in genetic associations based on the clinical subtype of MS.(7)

The average age of disease onset for ROMS is ~30 years while ~40 years is the mean age of onset for PPMS and SPMS progression.(2, 3) In large natural history studies, the SP and PP patients both tend to have lower extremity motor symptoms at onset of progression and rates of disease progression are similar, though SP patients do accumulate disability a bit faster.(4, 6) These reports have also shown that the age at higher disability thresholds is similar between RO and PP patients.(6, 8) From a

statistical and population based standpoint, these findings suggest that MS disease course and prognosis may simply be age-dependent and that a unique variation on inflammatory processes underlies the development of progressive disease.(4, 6)

Though MS is generally accepted today as a single disease with significant heterogeneity, from a clinical standpoint RO and PPMS are distinct entities. The dissimilarities between PP and RRMS suggest important pathophysiologic differences. On the other hand, PP and SPMS share many similarities, raising the possibility of similar pathophysiology leading to any form of progressive disease. Indeed, the acute relapse is dependent on significant inflammatory episodes while progressive disease is more a result of neurodegeneration.(2, 3) It is important to understand the unique nuances of the MS subtypes in order to develop effective therapies and provide the best patient care possible.

PPMS is a topic of particular interest as no effective therapy for PPMS is currently available.(5, 9, 10) PPMS is characterized by high neurodegenerative impact and the lowest inflammatory impact on disability.(3) Though there are focal white matter plaques, the number of classical active white matter lesions is low. Instead, there is extensive demyelination of the cerebral cortex and diffuse axonal injury in the normal-appearing white matter in the setting of a global, mild inflammatory state.(11) Overall, PPMS pathology reflects a classical inflammatory disease in which persistent inflammation is associated with axonal injury.(12)

Magnetic resonance imaging (MRI) findings are compatible with the pathological observations in PPMS. PPMS has a smaller lesion load and fewer gadolinium-enhancing lesions compared with ROMS, though the lesions still appear in classic periventricular, juxtacortical, and infratentorial locations. About half of PPMS patients have evidence of diffuse mild hyperintensity on T2-weighted imaging, reflecting the low level global CNS inflammation. Furthermore, cortical demyelination and neurodegeneration are reflected as diffusion abnormalities in healthy appearing grey and white matter and progressive atrophy that is most pronounced in the deep grey matter.(3) Notably, cervical cord atrophy is associated with disability and only seen in PPMS.(13)

Interestingly, MRI changes are known to occur at least 10 years prior to clinical

presentation of PPMS. This suggests that there may be a subclinical period of inflammation and disease activity preceding clinical progressive disease until a specific threshold of neurodegenerative damage is reached.(14)

The majority (80%) of PPMS patients present with progressive spastic paraparesis, typically in the lower extremities.(3) Unfortunately, despite the recent proliferation of immunomodulatory treatments targeting RRMS that have been approved by the FDA, no effective therapy for PPMS is currently available although some trials for progressive disease are ongoing.(5, 9, 10) Careful study of PPMS demographic characteristics and disease progression, clinically evaluated by disability accumulation based on the Expanded Disability Status Scale score (EDSS, scale ranges 1-10, Appendix A) (15), is important to improve patient diagnosis and care and to help design randomized clinical trials targeting the PPMS population.(16)

Though natural history studies of PPMS have been conducted (17), it is difficult to study large cohorts and accurately portray the course of PPMS as PPMS is only a small subgroup of the total MS population. In addition, many of the past studies characterizing PPMS or progressive-onset patients may have included patients diagnosed with PPMS prior to the introduction of stringent McDonald diagnostic criteria.(18, 19) As well, patients often did not present to the clinic early in the disease course.(20) Overall rates of disease progression are not clear, especially given recent data suggesting these may be changing with time or geographical location.(21, 22) The need for better estimates of the rate of disease progression in PPMS was highlighted when a recent clinical trial for glatiramer acetate in PPMS was terminated because short-term disease progression, measured by disability accumulation, was slower than anticipated (23) based on prior studies.

Two recent studies from large French cohorts suggested that MS disability accumulation consists of two independent phases, with Phase 1 being the duration from disease onset to EDSS=3 or =4 and Phase 2 being the duration from EDSS =3 or =4 to EDSS=6.(6, 24, 25) Progression through Phase 1 was highly variable while median Phase 2 progression seemed consistent in length from 6-9 years regardless of Phase 1 length.(25) The influence of risk factors also differed between the phases.(24, 25) However, this two-stage model has been sparsely validated in well-defined PPMS

patient populations.

Few studies have focused on PPMS disease progression, particularly in a modern cohort with widespread use of immunomodulatory therapies. For this study, the rate of disability progression in PPMS was investigated in a well-characterized, modern cohort that is longitudinally and prospectively followed at the Partners Multiple Sclerosis Center in Boston, MA as part of the "Comprehensive Longitudinal Investigation of Multiple Sclerosis at the Brigham and Women's Hospital" (CLIMB study). Furthermore, the time to six-month sustained progression, a measure that may be useful for future clinical trial design, was estimated and used to generate sample size calculations for hypothetical PPMS trials.

A report of this work has been previously published and the complete citation is found in the references section.(26)

Methods:

Subjects

The CLIMB is a longitudinal prospective study, established in 2000, of MS patients followed at the Partners MS Center, Brigham and Women's Hospital.(27) All patients seen at the Partners MS Center are offered enrollment in CLIMB. More than 80% of the active (clinical visit in past year) patients seen at this Center are enrolled in the CLIMB study. Inclusion criteria for the CLIMB study are: 1) diagnosis of MS or clinically isolated syndrome (CIS); 2) willingness to participate in a longitudinal study with biannual clinical visits and annual blood draws; 3) ability to complete annual MRI at the Brigham or equivalent facility. Patients are seen every six months and have detailed demographic, clinical, immunological, and MRI data validated and prospectively recorded in an Oracle-based electronic relational database. MS diagnosis is made by an expert neurologist based on the McDonald diagnostic criteria and available subjective and objective data.(18, 19) Patients in the CLIMB study with a definite diagnosis of MS were included in our query on November 11, 2012. To ensure use of up-to-date diagnostic criteria, patients with a most recent visit prior to 2010 were not included in the study. The CLIMB patients were classified as either PPMS or ROMS, which includes RRMS and SPMS, based on the physician diagnosis. Of the 73 PPMS patients, 70 (96%) fulfilled the McDonald 2010 criteria for PPMS. Two patients did not meet criteria due to a lack of data: no cord imaging or cerebrospinal fluid (CSF) studies within our system. One patient had normal spine MRI and CSF analysis but was felt to have PPMS because of the clinical presentation and abnormal brain MRI. One patient initially diagnosed with PPMS was found to have PRMS and was excluded from the PP cohort. Demographic characteristics of the PPMS and ROMS groups are presented in Table 1. To ensure that CLIMB PPMS patients were a representative sample of PPMS patients seen at the Partners MS Center, demographic characteristics of CLIMB PPMS patients are compared to non-CLIMB PPMS patients in Table 2.

Clinical markers and measures

The time to two main landmark EDSS values were investigated: EDSS=3 and EDSS=6. Based on previous work, the time from disease onset to EDSS=3 was defined

as Phase 1, and the time from EDSS=3 to EDSS=6 was defined as Phase 2.(25) Given the varied disease duration among the patients, the Multiple Sclerosis Severity Score (MSSS), which combines the EDSS and disease duration, was also calculated for the last visit.(28)

In addition to specific EDSS landmarks, time to sustained disease progression was also investigated. Sustained progression was defined as an increase of at least 1.5 points on the EDSS for patients with a baseline EDSS=0, an increase of at least one point on the EDSS for patients with initial EDSS scores between 1 and 5 or an increase of 0.5 points for patients with initial EDSS scores of 5.5 or greater that were subsequently maintained or increased for at least 180 days. The date of sustained progression was defined as the visit date at which sustained progression began.

Statistical Analysis

Demographic characteristics, type of first symptom, and first symptom lesion localization were compared between the PPMS patients and the ROMS patients using Fisher's exact test and Wilcoxon rank sum test as appropriate. The same tests were used to assess if CLIMB PPMS patients were different from the general clinic PPMS population.

Time to EDSS=3 from disease onset (Phase 1), EDSS=6 from EDSS=3 (Phase 2), and EDSS=6 from disease onset was estimated in each group using survival analysis techniques appropriate for interval censored data,(29) because some patients reached the disability landmark prior to entry and others did not reach the disability landmark at the last visit. PPMS patients were compared to the ROMS patients using an extension of the log-rank test appropriate for interval censored data.(30) Age at each EDSS landmark was also estimated using the same interval censored technique. For all of these analyses, the first EDSS=3 or EDSS=6 was used to calculate the times; future reversions were ignored as likely temporary improvement. In line with prior studies (6, 24), time from onset to EDSS=4 and EDSS=7 were also estimated using a similar approach.

In addition to the times to disability landmarks, the rate of sustained progression among PPMS patients was estimated. The same survival analysis was also conducted

on subgroups with baseline EDSS <5.5 and EDSS ≥5.5 at first visit. Subsequently, sample size calculations were made for hypothetical PPMS trials powered at 80% and alpha=0.05, with the outcome being a decrease of 30%, 50%, or 70% in the proportion of patients with sustained progression at one, two or three years. The power calculation used Freedman's method and considered people who did not have sustained progression at the end of the trial as administratively censored. All statistical analysis was completed in the statistical package R (www.r-project.org) with the interval library (31) and the sample size calculations were made using the stpower routine in the statistical package STATA.

Standard protocol approvals, registrations, and patient consents.

Institutional Review Board approval was granted by Partners Human Research Committee.

Results:

Demographic features

Table 1 provides the demographics of the study groups. Only 4.5% (73/1614) of CLIMB MS patients had PPMS. This was similar to the proportion observed in our entire center (only 6% or 116/1933 of MS patients seen at the clinic between 2010 and 2012 had PPMS). There was no significant difference in race and ethnicity between the PPMS and ROMS groups; however the proportion of males was significantly greater in the PP group ($p<0.001$). The age at disease onset and age at first visit were significantly higher in the PP group ($p<0.001$ for each comparison). Clinical disability at first visit, evaluated by the EDSS, was significantly greater in the PP group compared with the RO group ($p<0.0001$). Notably, a high proportion (78.1%) of the PP group was treated with immunomodulatory therapy during their disease course.

Table 2 compares the demographic characteristics of the CLIMB and non-CLIMB PPMS patients. The MSSS was lower in CLIMB patients compared to non-CLIMB patients showing that CLIMB patients were slightly less disabled on average. No other significant differences between the groups were observed on any of the demographic or clinical variables.

Symptom onset features

First symptoms and their lesion localization were compared between PP and RO patients (Table 3). Motor symptoms at onset were significantly more common in PP patients ($p<0.001$), while sensory and visual symptoms at disease onset were significantly more likely in RO patients (sensory: $p<0.001$, visual: $p<0.001$). The chance of first symptoms affecting coordination, bowel/bladder control, fatigue, or cognition was similar between both groups ($p>0.05$ for all). Comparison of first symptom lesion localization revealed a higher proportion of PP patients with spinal cord location ($p<0.001$). RO patients appeared to have a greater chance of optic nerve ($p<0.001$) or brainstem/cerebellum ($p=0.01$) first symptom lesion localization (Table 3).

Time to EDSS milestones

The time between EDSS landmarks for both PPMS and ROMS is shown in

Figure 1. Median time for progression to EDSS=3 was 2.8 years for the PP group and 15.4 years in the RO group ($p<0.001$; Figure 1). Further analysis revealed that the median time from EDSS=3 to EDSS=6 was 4.8 years for the PP group and 10.7 years for the RO group ($p<0.001$; Figure 1). Finally, PPMS was associated with a shorter time to EDSS=6 (11.7 years) from onset compared with RO (32.2 years; $p<0.001$; Figure 1). The time to first EDSS=4 and first EDSS=7 were also significantly different between the two groups ($p<0.001$, Figure 2). Age at first EDSS=3 and EDSS=6 was older in the PPMS group compared to the ROMS group (Figure 3).

Sustained Progression

Time to sustained progression in the PPMS group was analyzed, and the Kaplan-Meir curve is shown in Figure 4. The median time to sustained progression was 4.85 years (95% confidence interval (CI) 2.89-8.35) for all PPMS patients. There was a statistically significant difference between the PPMS and ROMS groups in terms of the hazard of sustained progression (estimated hazard ratio=2.33; 95% CI: 1.70-3.21; $p<0.001$), and the difference between ROMS and PPMS remained after controlling for age. When stratified based on baseline EDSS, the median time to sustained progression was 4.60 years for patients with EDSS score <5.5 at first visit and 4.85 years for patients with EDSS score ≥5.5 at first visit.

Given the distribution of time to sustained progression in PPMS patients, sample size calculations for future trials in PPMS patients are reported in Table 4. Three levels of treatment effect were estimated for trial durations of one, two, or three years. As expected, the sample size decreased as the length of trial increased and/or the treatment effect increased.

Discussion:

PPMS is an understudied subtype of MS; however, it paradoxically has a more aggressive clinical course than ROMS. There are currently no approved therapies for PPMS, and none which have shown significant efficacy in slowing disease progression.(9, 10) This has been in part due to the limited knowledge of the disease mechanisms underlying progressive MS as well as the limited understanding of parameters for clinical trials to test agents.

Here, we describe the demographic and clinical characteristics of our CLIMB PPMS patients, which are similar to previous cohorts and are a representative sample of PPMS patients seen at our clinic. Studies such as ours will, in aggregate, help in identifying clinical trial outcome measures and sample sizes to conduct such studies. Our sample adds to the limited number of cohort studies conducted in the modern diagnostic era.(8, 21, 32) In contrast, there are currently at least five clinical trials targeting PPMS patients listed on clinicatrials.gov at the time of this Scholarly Project Report preparation. The sample size estimates listed in Table 4, based on our observations, may provide guidance for the conduct of clinical trials for this underserved group of MS patients.

Only 5% of patients in our sample were diagnosed with PPMS, which is lower than reported in Lyon, France (15.3%)(6, 24), Renne, France (21.7%)(25), British Columbia, Canada (10-12.4%)(21, 22), London, Ontario (19.7%)(33), Lorraine, France (8.8%)(34), South Wales Valley, UK (11.0%)(8), and Calgary, Canada (10.3%)(32). However, our PPMS patients are well defined by modern diagnostic criteria and PRMS patients were excluded, unlike previous studies.

Our PPMS cohort had a male:female ratio of 1.09:1, similar to previous studies (1:1.3 (6, 33, 35, 36), 1:1.4(25), 1:1.13(21, 22), 1:1.12 (32), 1:1.1(8)). Mean age at onset (44.4 years) was higher than past reports (38.5-43.9 years).(6, 8, 21, 22, 25, 33) This may reflect problems with identifying true onset based on patient recall or population and geographical differences. As expected, both percentage male and onset age were significantly higher in the CLIMB PPMS patients compared to ROMS patients.

Despite the difficulty in ascertaining the true onset in PPMS, most studies agree with our findings of preponderance for motor symptoms at onset in PPMS versus RO

individuals and the greater proportion of RO patients with sensory or visual symptoms, including optic neuritis, at onset.(6, 8, 21, 22, 25, 33, 35, 36) Like other cohorts, this PPMS cohort exhibited a small fraction of patients with brainstem/cerebellar localization of first symptom.(6, 8, 21, 36) Importantly, a significantly greater proportion of PP versus RO had initial symptom localization in the spinal cord.(13)

Understanding progression of disability in modern PPMS patient populations is instrumental in designing successful trials. In this study, the median time to EDSS=6 was similar to more recent reports regarding the natural history of PPMS versus historical cohorts. Specifically, the median time in the CLIMB PPMS group was 12 years, which is similar to the times observed in recent cohorts (10.0 years in Renne(25), 14 years in British Columbia(21), and 9.6 years in Wales(8)), but was longer than historical cohorts that showed a median time to EDSS=6 of less than 9 years (6.0 years in Goteborg, Sweden(37), 7.1 years in Lyon(6, 24), and ~8.5 years in London, Ontario(33)). These data suggest slower disability accumulation in more recent cohorts, which may be a result of more modern diagnostic criteria, including MRI, allowing for earlier diagnosis or other changes in clinical care of patients over time.

Our results do not support the recently proposed two-stage model of MS disability progression, with progression through Phase 1 being highly variable and progression through Phase 2 being largely consistent regardless of Phase 1 length. In this model, disability accumulation is influenced by focal inflammatory lesions in Phase 1 and independent of focal inflammatory lesions during Phase 2.(6, 24, 25) As in other studies (6, 24, 25), our PP population had a significantly faster rate of progression from onset through EDSS=3 of disease compared to the RO group ($p<0.001$). Unlike prior studies, this cohort of PP patients progressed from EDSS=3 to EDSS=6 significantly faster than RO patients ($p<0.001$). Leray et al. previously reported significantly faster Phase 2 progression in progressive-onset patients as well, but the absolute difference of 0.8 years may not be clinically significant.(25) The CLIMB cohort had a greater absolute difference in Phase 2 progression rate (5.5 years), which we believe is clinically significant. Our data suggest that time through Phase 2 may not be so consistent among MS subtypes, implying that the two-stage disability progression model for MS may not apply to all subtypes of MS. However, the difference we note in Phase 2

progression compared to other reports may also be secondary to a better-performing modern ROMS cohort or the effect of disease modifying therapy as part of current standard of care.

We have more confidence in our data for Phase 2 progression because many patients are seen in the clinic during this time, while Phase 1 involves symptoms at onset, which are difficult to ascertain and subject to more biases. A unique two-stage disability progression model may exist for PP and ROMS, with long-term progression of irreversible disability modified by early use of disease modifying therapies, underscoring the possibility of fundamental biological differences in disease.

Koch et al. corroborated our finding that the proposed two-stage disability model does not apply in PPMS. In the original French ROMS cohorts, certain factors differentially influenced progression in the two phases- Phase 1 progression was associated with age at onset and sex while the same factors had no effect on Phase 2 disability accrual.(24, 25) However, in the Calgary, Canada PPMS cohort, progression throughout Phase 1 and Phase 2 was affected by the same factor, age at disease onset.(32) PPMS does not appear to be defined by two independent phases demarcated by the EDSS landmarks of EDSS=3 or =4 and EDSS=6.

Time to sustained progression in the CLIMB PPMS cohort (median time 4.85 years) differed from more historical studies. In the study by Weinshenker et al., time to sustained progression using a compatible definition was, by extrapolation, ~2.5 years.(38) More recently, Cottrell et al. presented median times to sustained progression stratified by baseline EDSS, ranging from 0.6 to 11.5 years.(39) Similar to other studies, progression was faster in the CLIMB PPMS cohort than the RO patients. Evaluation of time to sustained progression is particularly useful for design of clinical trials because it provides a shorter-term outcome measurement for therapeutic effectiveness.

The canonical paper that describes sample size calculations for PPMS clinical trials is by Cottrell et al., based on natural history data from the London, Ontario PPMS cohort (PPMS onset between 1928-1982).(39) However, recent clinical trials highlight the need for updated information on PPMS progression rates and measurements of sustained disease progression for trial design.

Harding et al. recently sought to inform PPMS trial design by generating power estimates, based on the South Wales Valleys PPMS cohort natural history, for theoretical trials using EDSS progression as the outcome.(8) However, sustained progression on the EDSS is a more appropriate outcome measure for PPMS trials to evaluate the effect of interventions on disability accumulation. Power estimates from Harding et al. are for potential trials in which all participants share a baseline EDSS score.(8) Such an approach would be very difficult given the low prevalence of PPMS and difficulty in establishing a diagnosis and would likely require more patients than a population-based approach. A population-based design approach also allows greater generalizability of trial findings.

Our data enable sample size calculations for PPMS trials in a modern patient cohort. Given the CLIMB PPMS progression rates, we estimated sample sizes for future trials and showed that larger studies may be necessary to observe treatment effects using the clinical outcome measures studied (Table 4).

The CLIMB PPMS cohort reflects a modern patient sample managed with current standard of care. The proportions of patients with sustained progression in one, two, and three years is similar between the CLIMB PPMS group and the placebo control PPMS group in the halted glatiramer acetate trial (CLIMB: 0.183, 0.27, 0.394; GA trial: ~0.20, ~0.32, ~0.48), suggesting that our patient data may be generalizable to the modern PPMS population and can provide new insights for clinical trial design. The rate of progression in CLIMB RRMS group has been described in detail in a previous publication.(40)

Limitations:

There are some limitations to our study. In addition to referral bias to our center, not all patients elected to participate in the CLIMB study, resulting in a smaller sample size of PPMS patients. However, the 73 PPMS CLIMB patients included in this study are comparable to the PPMS patients who are not enrolled in CLIMB (Table 2) and demographic characteristics of the CLIMB PPMS patients are similar to previous studies. Another limitation in this and other PPMS studies is the challenge in making an accurate diagnosis of PPMS, often resulting in a delay between first symptoms and the first study visit (9.4 years in this study) that may affect the patient's recall of disease onset. Additionally, since patients with PPMS often had substantial disability at the first CLIMB observation, our sample provided limited information regarding the exact disease duration at which subjects first reached EDSS=3 or =4. However, the interval-censored model used allows for inclusion of these patients in analyses of progression. Future studies that follow PPMS subjects from the initial symptom will be required to estimate the exact survival curve with more precision.

A limitation to the applicability of our findings, as in most natural history studies, is the use of EDSS as a marker of disability and disease progression. The EDSS scale is prone to inter- and intrarater variability.(41, 42) However, EDSS change currently remains the standard outcome measurement for clinical trials. Recent work using the CLIMB study has focused on alternative approaches for the analysis of progression data and the implications of this in terms of study design(43), but these alternative approaches are not commonly used in trials. Based on this previous work, we anticipate that the sample size requirements for trials using alternative outcomes will be reduced, but the amount of the reduction will depend on the analysis approach and the magnitude of the treatment effect.

We did not control for use of disease-modifying therapies in analyses of disease progression. This produces a clearer picture of disease natural history given the current standard of care and is particularly appropriate for studying PPMS because there is no proven disease-modifying therapy for PPMS. Furthermore, the efficacy of disease-modifying therapy on long-term progression of irreversible disability in ROMS is not well known.

Conclusions:

PPMS is an understudied population with no approved therapies. In light of recent clinical trials that failed due to controls progressing slower than predicted, there is a need for better assessment of PPMS natural history in the modern era to inform appropriate trial design. In this study, CLIMB PPMS patients were found to have similar demographic characteristics to previous cohorts and are a representative sample of PPMS patients seen at the Partners MS Center (Boston, MA). The time to EDSS landmarks in this study are longer than previously reported, but the difference between ROMS and PPMS remained highly significant and more importantly clinically meaningful. The time from EDSS=3 to EDSS=6, termed Phase 2 in previous studies, was found to be significantly different in PPMS compared to ROMS, which contradicts previous findings of similar time through this phase of disease. As such our data does not support the application of the proposed two-stage model of MS disability progression, based on progression to EDDS=3 and EDSS=6, in PPMS. Finally, the time to sustained progression showed that disease progression occurs at a slower rate in our sample than previously reported. Given this slower rate of progression, sample size estimates for future trials were estimated and showed that larger studies may be necessary to observe treatment effects using the clinical outcome measures studied.

Future Directions:

Future large single center and multicenter studies should assess the natural history of PPMS in the era of disease-modifying therapeutics in order to optimize the design of clinical trials in PPMS. They should validate and expand the small body of literature providing sample size and power estimates for future PPMS clinical trials. Ideally these estimates will be based on population-based PPMS cohorts and the outcome of choice, in line with current standards, will be sustained disease progression based on the EDSS. Such data is essential to designing successful trials that will hopefully yield therapeutics that slow PPMS disease progression.

While EDSS progression is the current outcome standard for trials, the EDSS scale is not ordinal and staying time at higher EDSS levels is significantly longer.(2, 8, 33) It is also prone to inter- and intrarater variability.(41, 42) Alternative outcome measures may be more helpful in following disease evolution over the short term. Furthermore, PPMS therapeutic trials based on alternative outcomes may require fewer subjects and less time. As such, future studies must focus on validating alternative measures of MS progression.

Finally, knowledge of prognostic factors is helpful in formulating treatment plans and providing care to PPMS patients. Several studies, with both retrospective and prospective design, have surveyed demographic and clinical variables as predictors of EDSS disability progression but findings have largely been inconsistent.(44) The most well-established prognostic factor for PPMS is age at disease onset. Findings from large PPMS cohorts in British Columbia, Canada(32), South Wales Valleys, UK(8), and Calgary, Canada(21) indicate that younger onset is associated with slower progression. Still, a study from Germany designed to validate reported prognostic factors did not find any variables predictive of PPMS disease progression.(44) It is clear that larger, multicenter studies are needed to assess the influence of demographic and clinical variables on PPMS disability progression. Furthermore, these studies should seek to evaluate the influence of environmental factors and biomarkers, such as vitamin D and immune markers, on PPMS disease course.

Acknowledgements

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Attributions

After surveying the available literature, I developed the specific aims for this project under the guidance of Dr. Chitnis. Data was queried from the CLIMB database at the Partners MS Center, which is managed by Mariann Polgar-Turcsanyi, MS. Dr. Carruthers helped validate clinical data and diagnosis for the PPMS cohort.

I designed the initial approach for data management and analysis. Dr. Healy helped develop the most appropriate statistical analysis methodology for our data and helped me understand the concept of interval-censored survival analysis. I completed an initial analysis of demographic/clinical characteristics and rates of disease progression with STATA. I also estimated time to sustained progression using Excel and STATA. Final survival analyses were completed in the statistical package "R" by Dr. Healy. Dr. Healy and I independently used STATA to estimate sample sizes.

After completion of the project, I wrote an initial manuscript and worked with Dr. Chitnis, Dr. Healy, and Dr. Carruthers to edit the manuscript and also respond to reviewers following submission for publication. The project ultimately resulted in a publication in *Multiple Sclerosis Journal.*(26) For this final Scholarly Project Report, I significantly expanded components of the published paper.

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Tables and Figures:

Table 1: Demographic characteristics of the patients

	PP	RO	p Value
N	73	1541	-
Male, %	52.1	25.7	<0.001*
White/Caucasian %	93.2	91.4†	1*
Hispanic/Latino %	1.4	3.6 ‡	0.51*
Age at onset, mean(SD)	44.4 (9.6)	32.7 (9.9)	<0.0001#
Time to first visit, mean(SD)	9.4 (7.4)	7.6 (8.7)	0.042#
EDSS at first visit, mean(SD)	4.1 (1.9)	1.9 (1.7)	<0.0001#
Ever treated, %	78.1	91.4	0.0006*

*Fisher's exact test
#Wilcoxon rank sum test
†28 patients had unknown or unreported race and did not contribute to analysis
‡22 patients had unknown or unreported ethnicity and did not contribute to analysis
PP: primary progressive multiple sclerosis
RO: relapsing-onset multiple sclerosis
EDSS: Expanded Disability Status Scale

Table 2: Demographic characteristics of CLIMB PPMS patients compared to non-CLIMB PPMS patients

	CLIMB	non-CLIMB	p Value
N	73	116	-
Male, %	52.1	44.8	0.37*
White/Caucasian %	93.2	88.7	0.44*
Hispanic/Latino %	1.4	1.9	1*
Age at onset, mean (SD)	44.4 (9.6)	43.8 (11.2)	0.78#
Age at last visit, mean (SD)	60.4 (7.9)	57.8 (10.5)	0.17#
EDSS at last visit, mean (SD)	5.1 (2.2)	5.7 (2.2)	0.16#
Disease duration from first symptom at last visit, mean(SD)	15.4 (8.5)	13.5 (8.6)	0.13#
MSSS at last visit, mean (SD)	5.9 (2.6)	6.7 (2.5)	0.01#

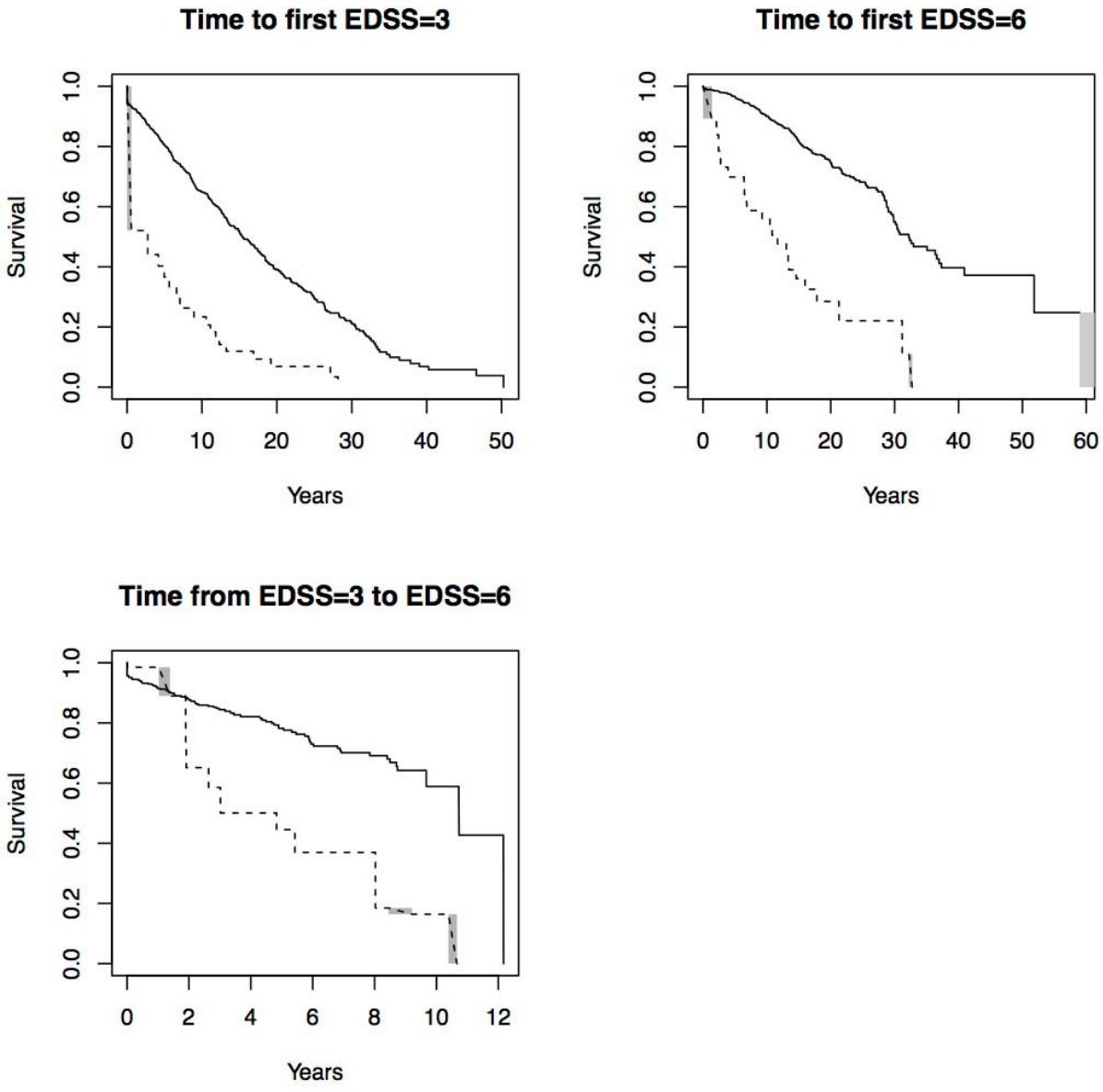
*Fisher's exact test
#Wilcoxon rank sum test
EDSS: Expanded Disability Status Scale
MSSS: Multiple Sclerosis Severity Score

Table 3: Clinical Characteristics of first symptoms

	PP	RO	p Value
First symptom, n(%)			
Visual	1 (1.4)	400 (26.0)	<0.001
Motor	55 (75.3)	325 (21.1)	<0.001
Sensory	16 (21.9)	805 (52.2)	<0.001
Coordination	6 (8.2)	150 (9.7)	0.84
Bowel/Bladder	5 (6.8)	46 (3.0)	0.08
Fatigue	1 (1.4)	66 (4.3)	0.36
Cognitive	0 (0)	33 (2.1)	0.40
Encephalopathy	0 (0)	1 (0.1)	1
Other	1 (1.4)	136 (8.8)	0.02
None of the above	3	139	
First symptom location, n(%)			
Optic nerve	0 (0)	342 (22.2)	<0.001
Brainstem/cerebellum	8 (11.0)	368 (23.9)	0.01
Cerebrum	4 (5.5)	201 (13.0)	0.07
Spinal Cord	43 (58.9)	613 (39.8)	0.001
Not Defined	24 (32.9)	135 (8.8)	<0.001
None of the above	1	139	

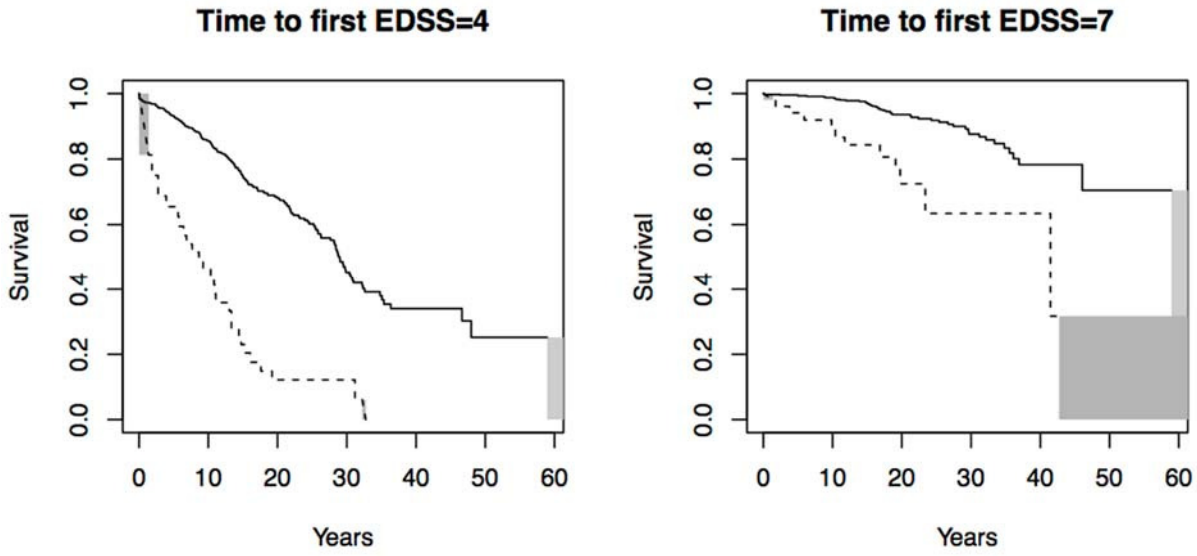
PP: primary progressive multiple sclerosis
RO: relapsing-onset multiple sclerosis

Figure 1: Estimated survival curves for time through Phase 1, through Phase 2, and onset to EDSS=6



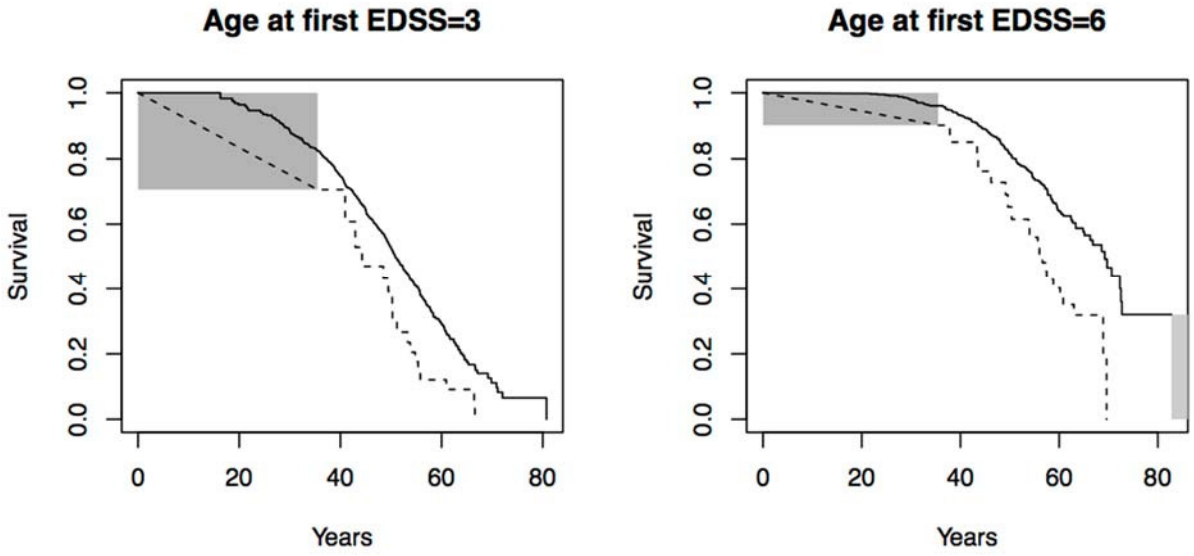
Dashed line: primary progressive MS, Solid line: relapsing-onset MS. Top left: Time from disease onset to first EDSS=3, Top right: Time from disease onset to first EDSS=6, Bottom left: Time from first EDSS=3 to first EDSS=6. Grey highlighted regions represent sections of the curve where there is uncertainty regarding the exact survival due to the interval-censored nature of the data.

Figure 2: Time from disease onset until first EDSS=4 and first EDSS=7



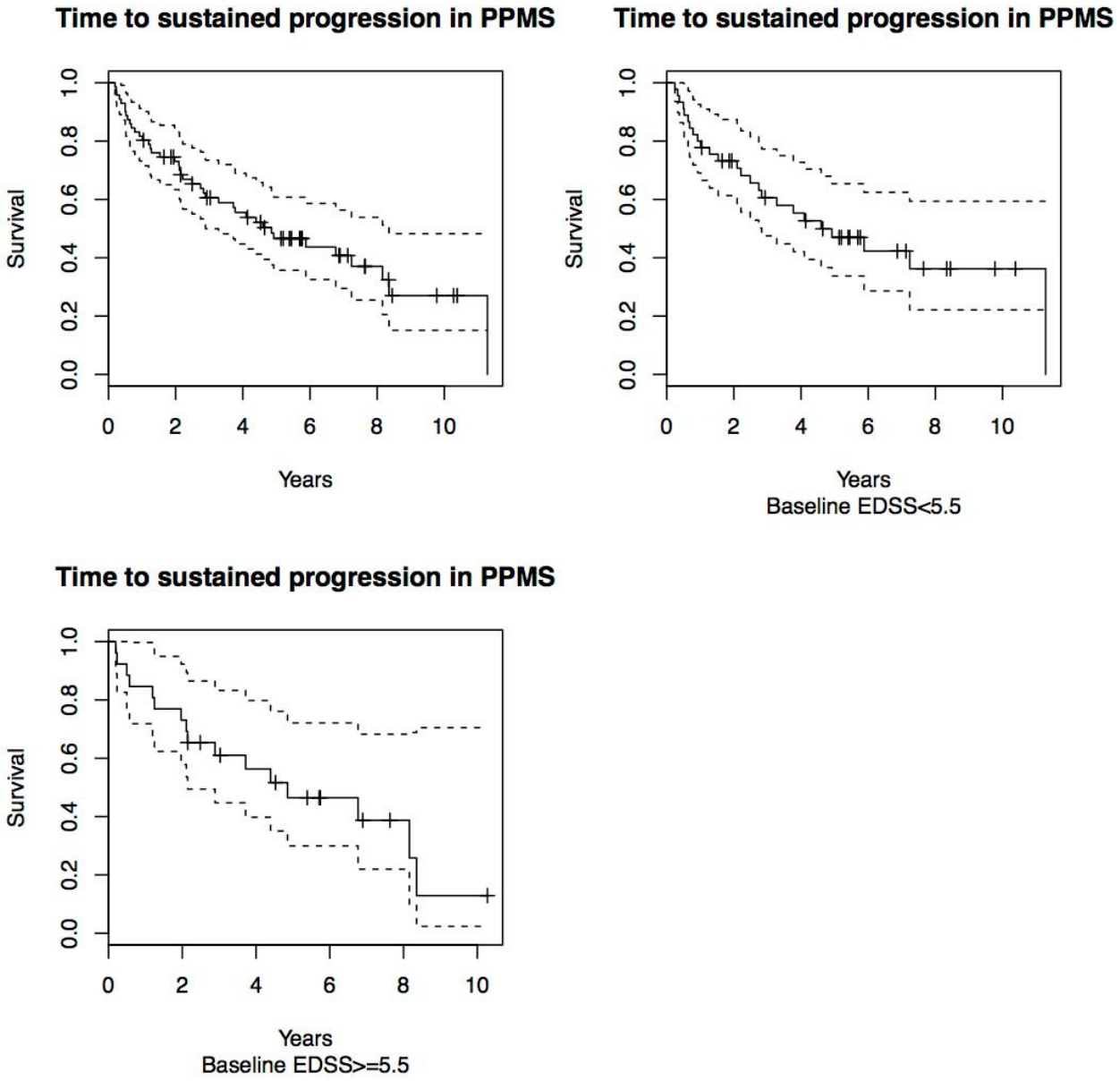
Dashed line: primary progressive MS, Solid line: relapsing-onset MS. Left: Time from disease onset to first EDSS=4, Right: Time from disease onset to first EDSS=7. Grey highlighted regions represent sections of the curve where there is uncertainty regarding the exact survival due to the interval censored nature of the data. Estimated median time to first EDSS=4 in PPMS was 8.7 years, and estimated median time to first EDSS=4 in ROMS was 29.0. Estimated median time to first EDSS=7 in PPMS was 41.7, and the estimated median time to first EDSS=7 in ROMS could not be estimated.

Figure 3: Age at first EDSS=3 and first EDSS=6



Dashed line: primary progressive MS, Solid line: relapsing-onset MS. Left: Age at first EDSS=3, Right: Age at first EDSS=6. Grey highlighted regions represent sections of the curve where there is uncertainty regarding the exact survival due to the interval censored nature of the data. Estimated median age at first EDSS=3 in PPMS was 44.3 years, and estimated median age at first EDSS=3 in ROMS was 50.8. Estimated median age at first EDSS=6 in PPMS was 56.6, and the estimated median age at first EDSS=6 in ROMS was 69.2.

Figure 4: Kaplan-Meir curve showing time to sustained progression of disease



Top left: Time to sustained progression for all PPMS patients, Top right: Time to sustained progression for PPMS with baseline EDSS < 5.5, Bottom left: Time to sustained progression for PPMS with baseline EDSS >= 5.5

Table 4: Kaplan-Meier estimates of time to sustained progression

Study duration (Years)	Estimated proportion with sustained progression in standard of care group	Hypothesized proportion with sustained progression in treatment group	Proportion change with sustained progression in treatment group	Sample size for 80% power
1	0.183	0.128	30%	1368
1	0.183	0.092	50%	446
1	0.183	0.055	70%	210
2	0.27	0.189	30%	850
2	0.27	0.135	50%	286
2	0.27	0.081	70%	136
3	0.394	0.276	30%	504
3	0.394	0.197	50%	174
3	0.394	0.118	70%	86

Note: Sample size calculations are for both groups assuming equal allocation in the two treatment arms.

Appendix A:

Kurtzke Expanded Disability Status Scale (EDSS) (15)

EDSS Score	Clinical Characteristics
0	Normal neurological exam (all grade 0 in Functional Systems (FS); cerebral grade 1 acceptable).
1	No disability, minimal signs in one FS (i.e., one grade 1 excluding cerebral grade 1).
1.5	No disability, minimal signs in more than one FS (more than one grade 1 excluding cerebral grade 1).
2	Minimal disability in one FS (one FS grade 2, others 0 or 1).
2.5	Minimal disability in two FS (two FS grade 2, others 0 or 1).
3	Moderate disability in one FS (one FS grade 3, others 0 or 1), or mild disability in three or four FS (three to four FS grade 2, others 0 or 1).
3.5	Moderate disability in one FS (grade 3) and one or two FS grade 2; or two FS grade 3 with others 0 or 1; or five FS grade 2 with others 0 or 1.
4	Fully ambulatory for some 500m without aid or rest and up and able to carry out full daily activities, but with relatively severe disability in one FS (one grade 4, others grade 0 or 1), or combination of lesser grades that exceeds the limits of prior stages.
4.5	Fully ambulatory without aid, up and about much of the day, able to work a full day but may otherwise have some limitation in full activity or require minimal assistance; characterized by relatively severe disability, usually consisting of one FS grade 4 (others 0 or 1) or combinations of lesser grades exceeding limits of prior steps. Able to walk without aid or rest for some 300 meters (975 ft).
5	Ambulatory without aid or rest for about 200 meters (650 feet); disability severe enough to impair full daily activities (e.g., to work full day without special provisions). Usual FS equivalents are one grade 5 alone (others 0 or 1) or combinations of lesser grades usually exceeding specifications for step 4.0
5.5	Ambulatory without aid or rest for about 100 meters (325 ft); disability severe enough to impair ability to work part-time without special provisions. Usual FS equivalents are one grade 5 alone (others 0 or 1) or combinations of lesser grades usually exceeding specifications for step 4.0
6	Intermittent or constant unilateral assistance (cane, crutch, brace) required to walk about 100 meters (325 ft) with or without resting. Usual FS equivalents are combinations with more than two FS grade 3+
6.5	Constant bilateral assistance (canes, crutches, braces) required to walk about 20 meters (65 ft). Usual FS equivalents are combinations with more than two FS grade 3+
7	Unable to walk beyond about 5 meters (16 ft) even with aid, essentially restricted to wheelchair; wheels self in standard wheelchair for a full day

	(12 hours) and transfers alone. Usual FS equivalents are combinations with more than one FS grade 4+ or very rarely pyramidal grade 5 alone.
7.5	Unable to take more than a few steps; restricted to wheelchair, wheels self but cannot carry on in standard wheelchair for full day and may need aid in transfers; may require motorized wheelchair. Usual FS equivalents are combinations with more than one FS grade 4+
8	Essentially restricted to bed or chair or perambulated in wheelchair, but may be out of bed itself much of the day. Retains many self-care functions and generally has effective use of arms. Usual FS equivalents are combinations, generally grade 4+ in several systems.
8.5	Essentially restricted to bed for much of the day. Retains some self-care functions and has some effective use of arm(s). Usual FS equivalents are combinations, generally grade 4+ in several systems.
9	Helpless bed patient who can still communicate and eat. Usual FS equivalents are combinations, mostly grade 4.
9.5	Totally helpless bed patient who is unable to communicate effectively or eat/swallow. Usual FS equivalents are combinations, almost all grade 4+
10	Death due to MS.